

NEUROCRITICAL CARE THROUGH HISTORY



Uremia and the Brain: The Contentious History of a Small Molecule

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The clinical state of uremia (and its encephalopathy) is considered toxic because there are circulating injurious metabolites entering the brain that are normally excreted in the urine—this conceptional explanation has not changed for more than a century [1]. Once dialysis was introduced, it provided indisputable evidence for the toxicity of some small molecular weight dialyzable compound, and, indeed, the most abundant organic solute is urea. Because urea is quantitatively the most important product of protein catabolism, it was also logical to regard uremia as a state of nitrogen overload (azotemia). It also translated into treatments with diets low in protein and high in carbohydrates and fats to extend the life of patients with end-stage renal failure.

Early researchers noted that impaired intellectual functions were a prominent feature of advanced renal disease. Removal of uremic solutes by dialysis was subsequently found to rapidly reverse this “uremic syndrome” [2]. It all suggested that exposure of brain cells to uremic solutes impairs mental function in patients with renal failure.

Understanding the Biochemistry of Urea

Friedrich Wöhler 1800–1882 synthesized urea, often heralded as the first organic substance belonging to the animal kingdom to be produced in the laboratory [3] (Fig. 1). From Berlin, Wöhler wrote to the revered J.J. Berzelius in Stockholm that “I can make urea without needing a kidney, whether of man or dog. The ammonium salt of cyanic acid is urea.” Once this molecule was considered the main culprit, the clinical features that characterized “uremia” were described and a full spectrum of a brain syndrome emerged, with (1) patients

progressing clinically from a mild impairment of intellect to deep coma; (2) extrapyramidal syndromes manifested by abnormal involuntary movements, tremors, rigidity, and asterixis; (3) increased neuromuscular irritability; and (4) a lowered seizure threshold [4, 5].

Is Urea the Responsible Molecule?

The significance of uremia in the pathogenesis of this clinical syndrome, however, has a long discombobulated history of medical advances—from the time of Richard Bright’s 1800s insight into retention of urea in kidney disease [6] to the modern era of renal replacement therapy for patients with end-stage renal disease. The clinical manifestations of Bright’s disease (nephritis) were now related to accumulation of urinary toxic components, principally urea in blood. The term *urémie* (uremia), was introduced in 1847 by Pierre Adolphe Piorry (1794–1879) [7]. The term azotemia, now almost abandoned, was a later entry derived from azote (the name for nitrogen) and was used by Antoine Lavoisier (1743–1794) to indicate the air component that could not sustain life. Because the concentration of urinary toxins was measured from its nonprotein nitrogen content in the blood, the term *azotémie* (azotemia) entered medical parlance and was used for elevated blood urea nitrogen levels, particularly in clinically asymptomatic patients who could go on to develop uremia.

The Clinicopathologic Description

The German pathologist Friedrich Theodor von Frerichs published a monograph in 1851 which focused more on the *Uramische Intoxikation* and its clinical signs and more than what happened to the kidney. His treatise is a medical classic, although the chemical data on which it was based were shaky: the rise of blood concentration of urea was unpredictable, and he mistakenly considered

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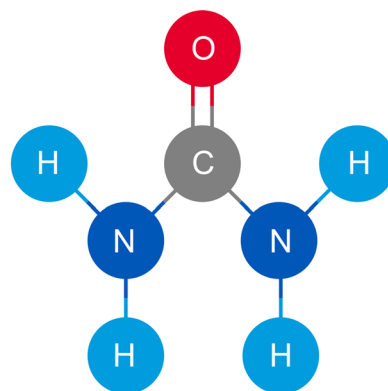
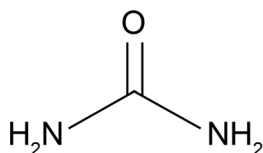


Fig. 1 Urea molecule

that ammonium carbonate, which he also found in the blood, was responsible for the toxic effects of uremia.

A century later, Baker and Knutsen divided the symptoms of uremia roughly into two groups: “those of depression of the central nervous system, such as apathy, muscular weakness, stupor and coma; and those of neuromuscular hyperexcitability, namely, increased tendon jerks, muscular twitchings, and convulsions.” They noted the patient was fatigued and unable to concentrate, and with progression of the disease the patient was more apathetic, with sleep being interrupted by restlessness and insomnia. Speech became unintelligible. Symptoms of neuromuscular hyperexcitability, such as “fibrillary muscular twitchings,” were present. The convulsions usually appeared late and were generalized. Focal or Jacksonian seizures could occur (and still be present after correction of uremia), and occasionally these epileptiform seizures continued even after the patient had recovered from the uremia.

Monoplegias, hemiplegias, aphasias, and apraxias were all observed. Baker and Knutsen [8] wrote, “Of the motor symptoms, hemiplegia is the most frequent. This usually is of a flaccid type and is often ascending, producing Landry’s type of paralysis. The involvement is transient, lasting hours or days and then disappearing, only to return after a variable period. Two of our patients had such episodes; in one the involvement implicated all limbs, resulting in quadriplegia.”

Previous pathology studies on brains in patients with uremia showed demyelination and included large areas of the white matter, but there were widely divergent lesions and other factors (ischemic insults) may have played a role. In the acute illness, the predominant alteration occurred within the cortical neurons, which

revealed an acute change in the nerve cells. In the more chronic illness, the most striking changes were parenchymal rather than neuronal and consist of focal and perivascular areas of demyelination and necrosis.

The key article (Fig. 2) for medical historians to consider was “a pathoanatomical study of brains of 104 patients dying in renal insufficiency with reference to the influence of complicating factors” published in 1961 [9]. The Danish pathologist Steen Olson found in nearly all the brains a well-characterized neuronal degeneration. Some localizations were more frequent and most severely affected, and these were, in no particular order, the sensory nuclei of the brain stem, the reticular formation, and the cerebral cortex. However, the Purkinje cells, the nucleus caudatus, claustrum, the thalamus, the globus pallidus, the putamen, the hypothalamus, the hippocampus, and somatic efferent nuclei were morphologically unaffected. They concluded:

Summarily, it may be said about the pathoanatomic changes in the brain in so polymorphous a material as the one described that the eliciting factors and the complicating conditions highly influence the picture. In the frequent cases of acute ischemic anuria we must especially reckon with the interference of circulatory failure, which not only causes injury to the renal parenchyma, but also, which is just as important for the patient, often gives rise to brain lesions [9] (emphasis added).

Experiments

Brennan and Plum used a cerebrospinal fluid (CSF) model for patients with uremic encephalopathy after earlier reports (Monck in 1949; Fig. 3) showed transient ataxia and reduced activity in dogs with CSF of patients with severe uremia injected into the ventricles [10]. In

STEEN OLSEN

THE BRAIN IN UREMIA

A PATHO-ANATOMICAL STUDY OF BRAINS
FROM 104 PATIENTS DYING IN RENAL
INSUFFICIENCY, WITH REFERENCE TO THE INFLUENCE
OF COMPLICATING FACTORS,
ESPECIALLY ISCHEMIA OF THE BRAIN

MUNKSGAARD . COPENHAGEN . 1961

Fig. 2 Olson's neuropathology

Symptômes d'urémie par injection intracisternale de liquide céphalo-rachidien d'urémiques chez le chien

Par P. De Munck

Fig. 3 Munk classic experiment

rats, ataxia occurred and marked the reduction of activity (nocturnal running) and "decreased desynchronization following arousal by auditory stimulus on electroencephalographic recordings." Later, it was found that CSF levels of many uremic solutes are normally kept lower than plasma ultrafiltrate levels by the action of the blood-brain and blood-CSF barriers. These barriers, however, cannot prevent accumulation of uremic solutes in the CSF when the kidneys fail [11, 12].

How Much More Do We Know Now?

Uremic encephalopathy remains a mysterious encephalopathy with a large number of confounders. These are hypertension and hypotension, dialysis, and traumatic brain injury from falls with concomitant thrombocytopenia and previous seizures. Occasionally, patients with posterior reversible encephalopathy syndrome or acute or chronic subdural hematoma are misdiagnosed as having uremic encephalopathy. The pathophysiology of uremic encephalopathy remains unclear and is likely a combination of accumulation of neurotoxins, such as uric acid, amino acids, myoinositol, and guanidino compounds. Because blood levels of parathyroid hormone, insulin growth hormone, glucagon, and gastrin are elevated, these hormones could also be implicated. We have come to understand that abnormalities in brain dopamine and serotonin

may play a role in the more severe cases of uremic encephalopathy. Acute uremic state is an important factor that influences a variety of neurochemicals, such as the biogenic amines (norepinephrine, epinephrine, histamine, and 5-hydroxytryptamine), and brain areas, such as stress-sensitive forebrain areas, neuronal cell groups involved in the regulation of water and electrolyte homeostasis, and central autonomic cell groups. Animal studies comparing acute uremic encephalopathy with hepatic encephalopathy have demonstrated an increase in brain inflammation in conjunction with an increase in vascular permeability in uremic encephalopathy. Local kidney injury may activate cytokines that cross the blood–brain barrier or activate other messengers that contribute to neuronal dysfunction. Alternatively, the retention of uremic solutes may trigger both the inflammatory reaction and neuronal dysfunction.

We have now a better understanding of the biomarkers and biochemical changes in uremic encephalopathy. Dialysis remains the only option to document improvement of clinical signs, and for many clinicians it is the disappearance of asterixis [13, 14]. Asterixis is a type of negative myoclonus characterized by sudden irregular lapses of posture of various body parts due to involuntary interruption in muscle contraction. The term was coined by Raymond Adams and Joseph Foley (with the help of a classics scholar). Just as in liver disease, it is a key clinical marker of uremia. Astute nephrologists look for it before and after dialysis.

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